Sucrose
A Literature Review
Prepared By:
WARF Institute, Inc.
Madison, Wisconsin
R E V I S E D

186

A revised copy of a literature review prepared by WARF Institute, Inc. In Madison, Wisconsin on **Sucrose** 8/74

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The Sugar Association, Inc.

1511 K Street, N. W. Washington, D. C. 20005

J. W. Talem, Jr.
President

September 19, 1974

Dr. George W. Irving, Jr.
Chairman
Select Committee on GRAS Substances
Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014

Dear Dr. Irving:

This is to accompany three copies of the "revised" Sucrose Literature Review prepared for us by WARF Institute. You will recall that we delivered three copies of the "unrevised" Review to your office on August 30.

Retrospectively, we discovered that the "unrevised" copies contain an undue number of typographic errors. None of these is substantive, but many of them are irritating to the reader. We are, therefore, hopeful that it will be practicable to discard the "unrevised" copies you have on hand and substitute the accompanying, more readable copies.

If, on the other hand, it is no longer feasible to make this substitution, no harm will be done; there is no possibility that any of the typos are of a nature that will mislead scientist readers.

We are sending three copies of the "revised" Review to Mr. Spiher as well.

Please forgive this additional imposition on your time.

Sincerely,

David J. Severn

DAVID J. SEVERN
Assistant to the President

DJC/cgf

Enclosures

cc: Mr. A. Spiher, FDA

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SUCROSE

A Literature Review

Prepared for:

The Sugar Association, Inc.
Washington DC

Prepared by:

WARF Institute, Inc.
Madison, Wisconsin

August 1974

Sucrose

Table of Contents

V. Specifications

A. Joint FAO/WHO Food Standards Programme, Codex Alimentarius Commission, CAC/RS 4 (1968). Recommended International Standard for White Sugar.

1. SCOPE

This standard applies to white sugar except that paragraph 3.1.4 (loss on drying) does not apply to white sugar in lump or cube form or to crystal candy sugar (crystal korizato) or to rock sugar (korizato).

2. DESCRIPTION

White sugar is purified and crystallized sucrose (saccharose).

3. ESSENTIAL COMPOSITON AND QUALITY FACTORS

3.1 Specification A

3.1.1	Polarization	not less than 99.7°
3.1.2	Invert sugar content	not more than 0.04% m/m
3.1.3	Conductivity ash	not more than 0.04% m/m
3.1.4	Loss on drying (3 hours at 105°C)	not more than 0.2% m/m
3.1.5	Colour	not more than 60 ICUMSA units

3.2 Specification B

3.2.1	Polarization	not less than 99.5°
3.2.2	Invert sugar content	not more than 0.1% m/m
3.2.3	Conductivity ash	not more than 0.1% m/m
3.2.4	Loss on drying (3 hours at 105°C)	not more than 0.1% m/m
3.2.5	Colour	not more than 150 ICUMSA units

4. FOOD ADDITIVES

4.1 Sulphur dioxide

Specification A	not more than 20 mg/kg
Specification B	not more than 70 mg/kg

5. CONTAMINANTS

Specifications A and B

5.1 Arsenic (As)	not more than 1 mg/kg
5.2 Copper (Cu)	not more than 2 mg/kg
5.3 Lead (Pb)	not more than 2 mg/kg (temporarily endorsed)

6. HYGIENE

It is recommended that the products covered by the provisions of this Standard be prepared in accordance with the appropriate sections of the General Principles of Food Hygiene recommended by the Codex Alimentarius Commission (Ref. No. CAC/RCP 1-1969).

B. NAS/NCR Standard for White Sugar

1. DESCRIPTION: A white, free-running, easily soluble granular powder having a good sweet flavor, free from burnt off-flavors or odors.

2. ESSENTIAL COMPOSITION:

a.	Moisture	0.05% maximum
b.	Sucrose Assay	99.90% minimum
c.	Sieve Analysis (5 minute Rotap)	5 to 20% thru US #80 screen
d.	Extraneous Matter	
	Macro	None
	Micro	None

3. MICROBIOLOGICAL EXAMINATION:

a.	Standard Plate Count	1000/g maximum	
b.	Yeast-Mold Count	100/g maximum	
c.	E. coli	Negative	
d.	Thermophilic Spore Count, NCA Method		
	Aerobic, maximum	5 Spls/Lot	Average
	Total Thermophiles	150/10g	125/10g
	Flat Sour Type	75/10g	50/10g
e.	Anerobic, maximum		
	Sulfide Producers	2 Spls +	10/10g
	Gas Producing	3 Spls +	4 of 6 tubes

C. NAS/NCR Standard for White Sugar

1. DESCRIPTION: An off-white, clear, sweet tasting, viscous liquid produced from No. 2 grade raw cane sugar.

2. ESSENTIAL COMPOSITION:

a.	Solids	67.0 ± 0.2° Brix
b.	Invert Sugar	0.4% maximum
c.	Ash	0.04% maximum
d.	pH (10% solution)	6.8 ± 0.2
e.	Color	0.20 to 0.35 Horne Color
f.	Clarity	Clear
g.	Flavor and Odor	Characteristic sweet flavor; free from any objectionable foreign flavors and odors.
h.	Extraneous Matter	none

3. MICROBIOLOGICAL EXAMINATION:

a.	Standard Plate Count	1000/g maximum
b.	Yeast-Mold Count	100/g maximum
c.	E. coli	Negative

IV. Description

A. General Characteristics

Monoclinic sphenoidal crystals, crystalline masses, blocks or power; sweet taste; stable in air; hygroscopic when finely divided, absorbing up to 1% moisture which is given off when heated to 90 degrees. Decomposes 160-186 degrees, chars or caramelizes.

B. Physical Properties

Soluble in H_2O, 1 gram/0.5 ml or in about 0.2 ml boiling H_2O; soluble, 1 g/170 ml alcohol or 100 ml methanol. Moderately soluble in glycerol or pyridine. Does not reduce Fehling's solution, form an osazone, or show mutarotation. Dilute acids and invertase hydrolyze sucrose to glucose plus fructose, or "invert sugar". Sucrose can be fermented, but resists bacterial decomposition as concentrated solutions.

Further elaboration of the chemistry of sucrose is provided in a paper by Fewkes et al (514) which may be found in the documents section of this monograph. The formation of sucrates and complexes as a consequence of the week polybasic acid behavior of sucrose is noted as are the derivatives resulting from the polyhydric alcohol nature of sucrose, e.g., ester, and urethanes.

VII. Analytical Methods

Polarimetric and chemical analyses may be found in Methods of Analysis, AOAC, Sections 29.025, 29.026, 29.031 and 29.032.

A isotope dilution anaytical method, modified to use a liquid scintillation counting technique, is described in a paper by McGagin and Eis (1127) and is included in this monograph (see for details).

VIII. Occurrence

Sucrose, commonly known as table sugar, is by far the most abundant carbohydrate found in the sap of land plants. It is one of the few organic compounds available in a state of unexcelled purity, in highly crystalline form, on a very large scale and at low cost. It has been produced since 2000 BC from the juice of the sugar cane and since the early 1800's from the sugar beet.

The combined annual world production of sucrose from sugar cane and beet was 83 million tons in 1972. Of this total the United States (including Puerto Rico) produces five million tons and consumes eleven million tons. Other major producing countries (in approximate order of size) are the USSR, Cuba, Brazil, India, France, Germany, Australia, Mexico and Taiwan.

Beets provide much of the sugar for Europe and central and western United States, and cane the rest. Other limited sources include sorghum and maple.

Sucrose is used by the food and other consumer goods industries as a basic nutrient (carbohydrate) and for sweetening, physical character and as a preservative. Of the eleven million tons consumed in the United States each year, 24% is sold in consumer-sized packages. The remainder goes to the baking, confectionery, ice cream, beverage, and other food industries. Pharmaceuticals, cosmetics, and other non-food users consume ninety thousand or so tons annually. The commercial utilization of sucrose chemicals is increasing. Only a handful of compounds are presently used by the chemical and allied industries or other non-food groups. Sucrose octaacetate and sucrose acetateisobutyrate are manufactured in substantial volume. Both esters are additives for specialty polymers, chiefly in adhesives. The octaacetate is a bitter chemical also used as a denaturant for alcohol. Cyanoethyl sucrose is manufactured on a limited basis for modification of specialty adhesives in the electronics industry. Mannitol is an important product in the food industry (792).

The Sugar Research Foundation has sponsored work on applications of sucrose chemicals. The most promising results have been obtained with sucrose ester detergents and surface coatings. Sucrose surfactants have been produced by a number of companies in the United States, Germany, Japan, and elsewhere. Although still under test, they show excellent promise as non-toxic, non-ionic, highly detersive agents. Sucrose-based surface coatings also exhibit good properties, particularly those made from sucrose linseedate. Various other polymers and plastics have been prepared or modified with sucrose (792).

Sucrose is synthesized by a number of bacterial enzymes from glucose-1-phosphate and fructose or from free glucose. The chemical synthesis was accomplished 20 years ago, and at best has yielded about 6% (514). A recent paper by Ness and Fletcher (1246) describes one technique for the synthesis of sucrose through the use of 1,3,4,6-tetra-O-benzyl-D-fructofuranose condensed with 2,3,4,6-tetra-O-benzyl-alpha-D-glucopyranosyl chloride, the preparation of which form a mixture of anomers of 2,3,4,6-tetra-O-benzyl-1-O-(p-nitrobenzoyl)-D-glucopyranose is described. The details of chemistry and chromatographical techniques may be seen by reference to the document section of this monograph (792).

Biological Data

1. Acute Toxicity

Rat

(Boyd et al (184), in a literature review found the data on acute toxicity on sucrose inadequate to answer their questions and conducted very thorough studies on the acute toxicity of sucrose in the rat. Adult, male Wistar albino rats, weighing 300 to 500 grams, were fed a commercial Purina diet and water ad libitum. Sixteen hours before administration of the sucrose, the animals were placed in separate metabolism cages and given only water. Varying solutions of sucrose in water were given at a constant volume dose of 60 mls per kilogram and the concentrations varied to provide sucrose dosages of 5 to 80 grams per kilogram. The lower and higher dosage levels were given to 16 to 20 animals per dose. A total of 19 different dosage levels were administered in addition to 48 control rats receiving distilled water only. Clinical measurements made daily, six days a week, for 2 weeks and followed by casual observations to one month, included urinalysis, autopsies performed on selected animals, gross and microscopic examination, organ weights and water content of specified organs.

There were no deaths in animals given dosages of 5 to 24 g/k, while all animals receiving 60, 70 and 80 g/k died within 5 hours. The LD 50 $\pm$ SE for all deaths from sucrose was 35.4 $\pm$ 7.0 g/k. A group of 30 female albino rats weighing 250 to 300 grams was tested in a similar manner and produced an LD 50 of 29.7 $\pm$ 3.7 g/k. Although this indicates sucrose is more toxic to the female, this data was not significant when examined at $P = 0.02$.

Clinical signs of hypokinesia, prostration, abdominal bloating and diarrhea were observed in groups receiving sucrose as well as those receiving water alone. Signs observed in sucrose groups were more severe and persistent. In addition, cyanosis was observed in animals receiving sucrose but not those receiving water. Pre-mortality signs observed in animals which died within 9 hours were tonic-clonic convulsions followed by stupor and respiratory failure. Increased urine volume and presence of reducing substances, calculated as glucose, and a decrease in urine pH were dose-related in the first 24 hours but not beyond that time period. No effect on daily urinary protein output was noted. Complete recovery was the rule in those animals that survived.

Post-mortem examination of those animals that died early from higher doses displayed marked gastroenteritis, arteriolitis, mild hepatitis, early nephritis, myocardytis and capillary and venus congestion of the brain and meninges.

These acute deaths were believed to result from the congestion of the brain and meninges. Death from doses smaller than the LD 50 occurred mostly within the 10 to 48 hour period following anorexia, severe diarrhea, loss of weight, hypothermia, diuresis, glycosuria, and aciduria. A post mortem examination of these animals revealed residual gastroenteritis and encephalitis, marked tubular nephritis, arteriolitis, focal necrosis of the myocardium, some adrenal hypertrophy and inhibition of spermatogensis. Some dehydration of organs seen in non-survivors had largely disappeared by two weeks and at one month organ weights and appearance were normal.

Constantopoulos and Boyd (336) studied the influence of several conditions on the acute toxicity of sucrose in the albino rat. Sucrose was given, dissolved in water, at various dose levels by intragastric cannula. The effect of food in the stomach, volume of vehicle, sex of the animal, body weight and age of animals and season on the acute single dose toxicity of sucrose in rats was studied. The influence of developed tolerance to sucrose and of dosing 5 versus 7 days per week was also studied. In reveiwing this work it should be noted that the above mentioned work of Boyd et al (184) involved the use of male rats weighing 300 to 500 grams which were dosed in an unstarved state. To study the effect of food in the stomach, male rats weighing 180 grams were fed until treated and the LD 50 determined to be 37.24 $\pm$ 7.3 g/k. Although this value was somewhat higher than that determined for male rats weighing 300-500 grams which had been starved, it was not a statistically significant increase. In this comparison one cannot ignore the probable effect of weight and size.

In studying the effect of volume of dose on the toxicity of sucrose, volumes of 35, 40, 45, 50, 55 and 60 ml/kg were given to male rats weighing approximately 176 grams. This study indicated that level of toxicity and volume of dose were directly related.

The effect of sex on the toxicity of sucrose was studied by dosing unstarved male and female rats weighing approximately 180 and 178 grams respectively. The results indicated that sucrose was slightly more toxic for the female and this agrees with the results noted by Boyd et al (184).

To examine the effect of body weight and age of animals on the toxicity of sucrose, two groups of unstarved male rats, one weighing approximately 118 grams and the other weighing approximately 182 grams were each given a single oral dose equivalent to 37.5 g/k of sucrose in a volume of 50 ml/k; the larger rats were four weeks older than the smaller rats. The mortality rate of 9.8% in the younger animals and 40% in the older animals differed significantly.

To examine the influence of season on the toxicity of sucrose, similar groups of male rats having body weights of 150-175 grams were treated with 37.5 g/k of sucrose. Separate groups were treated in January, February, March and June. No difference in the mortality rate was noticed between the summer and winter months.

To determine if the animals developed a tolerance to the toxicity of sucrose twenty unstarved rats were given daily doses of 37.5 g/k of sucrose, 5 days a week for 34 days, and there were ten survivors on the 35th day. The survivors were given 45 g/k of sucrose in a volume of 50 ml/k. This dose was estimated to be an LD 100. None of the pretreated rats died, while the same dose in a group of control rats, which had only received a daily water dose produced 85% mortality. These surviving primed animals were continued on a dosage schedule of 45 g/k, administered 17, 24 and 31 days after the original challenge; all but two rats survived. Although this experiment indicated the rats had developed a tolerance for sucrose, the possibility that a more resistant group had been selected in the initial dosing had to be considered. To test this premise a group of rats were dosed with 20 g/k per day, 5 days a week for 34 days. This dose did not kill any of the rats. On the 35th day, administration of sucrose at 45 g/k resulted in no mortalities. A similar group of control rats, which had received only water for the 34 days were treated with 45 g/k of sucrose and a mortality of 80% resulted. This proves that a tolerance to acute toxicity of sucrose can be developed in the rat.

To determine the influence of dosing daily and continuously compared to dosing 5 days per week with a two day rest period, a study was initiated involving two test groups of rats being dosed with equivalent total weekly dosage of sucrose: which in one case as administered in 5 days, and in the other case for the entire 7 days. Each test group had its own control group. Results indicated increased mortality in animals receiving the 5 day dose.

II. Short-Term Studies

RAT

Constantopoulos and Boyd (335) studies the subacute effects of sucrose and determined the LD 50 (100) days for sucrose given to rats. Male albino rats weighing from 150 to 175 grams initially were fed a standard Purina chow and water ad libitum. Sucrose was administered daily in doses ranging from 20 to 45 g/k given by intragastric cannula. Each dose was administered daily or until 60% mortality occurred in the specific group. The clinical data gathered initially second weekly intervals during sucrose administration included: body weight, food and water intake, calorie

consumption, colonic temperature, urinary volume, pH, glucose and protein. Gross and microscopic pathology were noted for all animals which died on test or were sacrificed at termination.

The observations noted on animals dying in less than one week, which were primarily in the high dose level groups, supports that data previously reported by Boyd et al on the acute toxicity of sucrose. The data collected on animals dying from 9 to 100 days of age is probably confused by malnutrition, resulting from the dilution of the basal diet; a laboratory chow, by the high level of sucrose. It is stated in the paper that the caloric intake was essentially the same for all groups; therefore, in those groups getting the high dose level of sucrose, their intake of chow was severely limited and protein, vitamin, and mineral deficiencies probably existed after the first portion of the feeding period. In contrast to this data recorded on toxicity of sucrose during a 100 day dosing period, many laboratories routinely use sucrose as the source of carbohydrate in subacute and chronic feeding studies. These studies will routinely use a diet containing sucrose at approximately 70% of the total diet dry weight. The daily dose for rats at various ages and levels of food consumption are noted in the following table:

Post weaning(wk)	Body wt(gm)	Daily Consumption		
		Food(gm)	Sucrose(gm)	Sucrose(gm/kg)
0	55			
1	75	.8	6.4	85
2	99	1.2	9.6	97
3	127	1.4	11.2	88
4	151	1.5	12.0	79

This data would indicate that animals survive and respond normally at levels of intake much higher than would be indicated by the 100 day toxicity study, Boyd, Constantopoulos et al.

Harper and Worden (708) reported the effects of fructose, sucrose and glucose when incorporated as the sole source of carbohydrate at approximately 80% of the diet of rats fed for a period of 26 weeks. Food consumption in all sugar groups was below that noted for the control group receiving a control diet. Groups receiving sucrose and fructose did not show a significant depression of weight gain, while the glucose group weights were significantly below those of the control rats. "External dimensions were uneffected, but fructose markedly increased heart, liver and kidney weight, liver

fat deposition and plasma cholesterol level; and reduced total carcass water, liver water and liver protein. Sucrose showed a similar, but less marked effect, due presumably to its fructose component, but glucose had on the whole effects of a lower order."

III. Long-Term Studies

Although sucrose has seldom been specifically studied for toxicity over the long-term or lifetime of animals, it has been frequently used as the carbohydrate portion of semi-synthetic diets used in toxicological studies. These diets would be similar to those referred to in the short-term protein quality studies and would generally contain approximately 70% sucrose. One will find in the literature a number of studies using such a synthetic diet, and in more recent years Friedman and co-workers have reported two chronic toxicity studies involving artificial sweetners in which sucrose diets were included. In these studies sucrose was fed at 67% of the diet. In the more recent study involving saccharin the animals were carried through a reproduction and the long-term or chronic portion of the study was conducted on F-1 animals (44A).

Munro and associates also have studied the artificial sweetner and utilized semisynthetic diets, which incorporated approximately 70% sucrose (83A).

Dalderup and Visser reported in 1969 a study showing the life span of Wistar male albino rats had been decreased in animals receiving 30% of their calories as sugar when compared to controls receiving 14.5% of their calories as sucrose. When they repeated this study, they found the effects were similar in the case of groups that received a sucrose diet, a control diet and a diet containing extra sunflower oil. Rats on diets containing dried meat or butter substituted for some starch in the human type diet lived less long than the control animals (35A).

Wogan and Newberne have also reported the use of sucrose at 14.7% of the total diet as part of the carbohydrate portion of a satisfactory basal diet used in chronic toxicity and carcinogenicity studies (114A).

IV. Carcinogenicity

Hueper (776) refers to a number of early workers reporting carcinogenic action and describes a study to determine the carcinogenic action of a number of sugars when injected subcutaneously. Included in this study was a group receiving twice weekly injections of 25% sucrose solution. In these studies there was no evidence that sucrose or any of the other sugar solutions cause carcinogenicity either at the site

of injection or systemically. The author suggests that previous findings may have been the result of contaminants present in the solutions injected. Since the studies described involved injection of the sugar solutions, it is questionable whether they are applicable to the safety evaluation of sugars that are to be consumed in the diet.

In the studies of Friedman et al (44A) and Munro et al (83A) previously referred to in the long-term study section, evaluation of tumor incidence and occurrence to determine if any of the substances being fed were carcinogenic was a major portion of the indepth toxicology protocol. In neither of these long-term studies on sweetners was there any indication of a carcinogenic activity attributable to feeding of sucrose. A number of other studies conducted to determine the carcinogenic potential of artificial sweetners have included sucrose diets as negative or experimental control. In no instance was sucrose incriminated as a possible carcinogenic chemical.

V. Reproduction

In an early study reported by Whitnah and Bogart (1876) three experimental diets differing only in the carbohydrate portion were fed to animals over a two-year period. In this study a diet containing starch at 50% was compared with two diets in which 40% of the starch was replaced by either sucrose or lactose. The data indicates that the reproduction among the lactose and starch fed animals was normal, while sucrose fed animals generally failed to reproduce. In the more recent study reported by Friedman et al (44A) no adverse effects on reproduction were reported. Unpublished data presented in the following table is from controlled reproduction studies incorporating control diets containing 64% sucrose and conducted at WARF Institute, Inc.

	Group 1	Group 2
**Fertility Index	85.0	90.0
**Mating Index	1.18	1.11
**Gestation Index	100.00	100.00
**Viability Index	93.0	96.0
**Survival Index	97.0	97.0
**Lactation Index	98.0	99.0
Av. No. Days to Mate	2.9	2.6
Av. No. Days Gestation	21.9	22.1
Av. No. Born/Litter	11.7	11.2
Av. Pup Wt. Day 4 (G)	8.7	9.1
Av. Pup Wt. Day 21 (G)	51.0	50.0

**Fertility Index=(No. Pregnancies/No. Matings) X 100
**Mating Index=(No. Copulations/No. Pregnancies)
**Gestation Index=(No. Litters with Live Pups/No. Pregnancies) X 100
**Viability Index=(No. Pups Born Alive/No. Pups) X 100
**Survival Index=(No. Pups Alive Day 4/No. Pups Born Alive) X 100
**Lactation Index=(No. Pups Alive Day 21/No. Pups Alive Day 4) X 100

In view of this data and the general successful use of high level sucrose in semisynthetic diets, any reports indicating sucrose had interferred with reproduction should be seriously examined with regard to other possible agents or conditions which may have caused the reproductive failure.

VI. Teratogenicity

A number of studies to determine the possible teratogenic effects of sucrose have been conducted. In the study by Klotzche (916) in 1969 he reports on several groups of pregnant white New Zealand rabbits receiving sucrose on the 6th to 18th day of 2, 4 and 10 g/k per day. On the 29th day animals were sacrificed and fetuses removed and examined. No evidence of teratogenic effects were noted in groups receiving sucrose.

In similar studies on rats and mice reported by Food and Drug Research Laboratories, Inc. (1980) they reported on animals receiving up to 1600 mg/k of sucrose for ten consecutive days. No effects on nidation, maternal survival, fetal survival or post-mortem abnormalities were noted.

VII. Cariogenicity

The role of diet, heredity and immunology in the development of dental caries has been an active area for research over several decades. This research consists of epidemiological and clinical studies in human population and laboratory studies involving in vitro research and invivo research in caries resistance and caries sensitive laboratory animals. Newbrun (1252), Dalderup (34A) and Hartles (56A) have published comparatively recent reviews of caries research. Newbrun emphasizes the laboratory aspects of the research, while Dalderup and Hartles concentrate more on the epidemiological and clinical human studies.

In general it is agreed that carbohydrate is essential in the oral cavity for the development of dental caries. The carbohydrate effect is apparently a local effect in the oral cavity and not a systemic or nutritional effect as long as other nutritional elements are maintained at an adequate level.

Dalderup (34A) reports that apart from carbohydrate importance, per se, the type of carbohydrate is also of extreme importance. He emphasized that the highly refined carbohydrates particularly related to an increase incidence of caries. Although some animal experimentation indicated that decreased caloric intake favored a decrease in caries incidence, this was considered probably due to a decrease in time of exposure of foods in the oral cavity. Studies in human populations have not been able to support the contention that decreased caloric intake

is related to a reduction in caries, but rather the reduction was related to less frequent exposure of the oral cavity to oral food, particularly between meals. Only if present in the form of a sticky type food was a high level of sucrose intake at meals related to an increased caries incidence. This emphasizes the need for long oral contact of the carbohydrate with the teeth to procude the cariogenic effect and supports the contention that consumption between meals is of prime importance. These effects have been experimentally supported in animal experimentation. In the past decade a great deal of effort has been directed toward the environment of the oral cavity and its relation to caries development. The presence of specific bacterial forms which convert the carbohydrate to polysaccharide, variations in the salivary enzyme activity, oral pH, salivary buffereing action and possibly even more subtle changes in the chemical environment of the mouth are all implicated in the caries story.

A review of Newberne (1252) implicates sucrose as "the archcriminal of dental caries." He first presents evidence of the extra-cellular biosynthesis of polysaccharide by an enxymatic action which has a particular specificity for sucrose as a substrate. Unlike intracellular bacterial synthesis of polysaccharide which involve an intermediate, such as sugar-1-phosphate or nucleoside diphophate-sugar, the extracellular synthesis appears to transform glucose or fructose units directly to the growing polymer. Although the actual mechanism involved is not described, the enzymes involved in the synthesis are discussed.

Newberne (1252) proceeds to supply the microbiological evidence that certain strains of oral streptococci can be shown to be cariogenic. A consistent feature of the streptococci is their ability to form extra-cellular polysaccharide and significantly more polysaccharide is formed from sucrose than from an equivalent amount of glucose, maltose, lactose or fructose, or glucose and fructose combined. Sucrose is further incriminated by invitro and invivo experiments, which indicate that cariogenic strains of oral micro-organisms required sucrose to produce plaque formation and were incapable of plaque formation in the presence of carbohydrates, such as glucose, fructose, galactose, lactose, sorbitol or a mixture of glucose and fructose.

A more recent review by Makinin (76A) covers the role of sucrose and other sugars in the development of dental caries. He summarizes that a number of micro-organisms can be involved in caries development but some are more cariogenic than others. Animal experiments have proven hard to standardize and obtain uniform results and it is anticipated that human studies will be more difficult. Sucrose is considered the most cariogenic of sugars with sugars rated in decreasing cariogenicity as follows: sucrose, glucose, (maltose, lactose, fructose) sorbital and xylitol. It is suggested that xylitol could have utilization

as a non-cariogenic sugar but any undesirable characteristic must be thoroughly examined before any widespread use of this nature. A number of new areas of interest regarding caries development, etiology and prevention are reviewed.

The leading position of sucrose among sugars as a cariogenic agent, however, is called to question by the results obtained by Bowen (Abstracts of Papers, 168th National Meeting, American Chemical Society, Atlantic City, New Jersey, September 8-13, 1974, CARB 044) in primates given glucose alone and fructose alone. Plaque formed in response to these sugars has substantial levels of polysaccharide and a high acidogenic potential. Bowen suggests that the belief that a substantial reduction in the prevalence of dental caries would occur if glucose or fructose were substituted for sucrose is unsupported by the evidence.

Although the role of sucrose in the development of caries has been substantially identified and developed, Glass and Fleisch (47A) in a more recent report on their studies of children and the consumption of sweetened cereals, does not support a direct connection between consumption of high sucrose cereals and increased caries development. Although some of the children participating in the study consumed large amounts of cereals containing up to 45% sucrose, no association was demonstrated between dental caries and this level of cereal consumption. Although these results seem to be inconsistent with the existing knowledge concerning caries etiology as demonstrated by animal studies, it should be remembered that earlier reports have stated that the consumption of sugars during the normal meal time did not appear to effect caries development, nor did the consumption of sucrose in non-sticky food materials appear to have any marked effect on the development of dental caries.

In summary, although the consumption of sucrose has been incriminated as being directly related to the development of dental caries, the conclusion of Glass and Fleisch (47A) fairly summarizes the present position with regard to the role of sucrose in the development of dental caries. "The cariogenicity of foodstuff may not be highly correlated with the surcose content alone. The time of eating, consistency of the food, and the conditions under which a particular food is eaten may be as significant as its sucrose content in the determination of its relative cariogenicity."

Present effort in solving the problem of cariogenicity emphasizes the bacterial role in plaque formation in caries etiology and the possible use of bacterial and immunological agents in the prevention of caries.

For more detailed information on the etiology of caries, the reader is referred to Charlton et al (25A), Fry et al (45A), Grenby (54A) (55A), and Stephen (105A) regarding papers on plaque formation and chemistry; to Esposito (485), Fitzgerald and Fitzgerald (41A), Jenkins and Tatevossigan (821), Hartles (56A), Tuoma et al (71A), Madsen (75A), Makinen (76A) and Stralfors (106A) regarding the effect of substances and conditions which affect caries development; and to Robrish (98A), Schachtele et al (99A) (100A), Keyes (63A) and Tanzer (107A) for information on the relation of microorganisms and dental caries. Scherp (101A) presents an abbreviated analysis indicating the most promising areas of investigation directed at the prevention of caries and emphasizing the microbiological aspects of caries etiology.

VIII. Heart Disease

In 1957 Yudkin (1932) presented an analysis of the data available in 15 countries regarding the correlation of heart disease and diet. In it he compared coronary mortality with rate of consumption of total fat, calories from fat, animal fat, butter fat, vegetable fat, margarine, total protein, animal protein, sugar and total calories. A comparison of heart disease and annual income was also included. He also analyzed data for the United Kingdom in which he correlated coronary mortality with fat intake, animal fat intake, vegetable fat intake, intake of margarine, sugar intake and the number of radio and television licenses in the United Kingdom. He summarizes his conclusions as follows:

> "A consideration of some of the more readily available data on the incidence of coronary death and on food consumption makes it difficult to support any theory which supposes a single or major dietary cause of coronary thrombosis.
>
> It is suggested that relative over-consumption of food associated with reduced physical exercise may be one of several causes of the disease."

In contradiction to this conclusion a number of authors (1A, 36A, 50A, 93A, and 767) reference this paper in support of the contention that sugar consumption is directly related to the occurrence of coronary mortality. This contradiction appears to be related to a single statement within the text of Yudkin's comparison between different countries in which he states, "There seems to be no relationship with the intake of total protein, but some relationship, about as good for total fat, with intake of animal protein. There is a better relationship with intake of sugar than with any other nutrient we have examined. The relationship with total caloric intake is about as good as that with the intake of total fat or of animal protein." Although this statement incriminates sugar, it is contrasted with a later statement in which he is comparing the increase in coronary mortality with increase in various

nutrient intakes for the United Kingdom. Here he states,

> "Sugar intake rose before the recent war with a rise of coronary mortality, but from 1940 to 1950 sugar intake was lower than before the war, although coronary mortality had doubled during that time.
>
> By far, the best correlation I have found with trends in coronary mortality is in the number of radio and television licenses."

Regardless of the conclusions drawn from this paper, it centered a great deal of attention and research on the relationship of sucrose and heart disease.

The effort to determine a causal relation between the consumption of sugar and coronary heart disease has produced a large volume of literature on epidemiological, human clinical and animal studies directed at the question and frequent literature reviews attempting to draw some reasonable conclusion from frequently contradictory results on what has become a very controversial subject.

Epidemiological studies have not generally supported the hypothesis that sucrose consumption is a major etiologic factor in heart disease. Paul et al (92A) reported an epidemiological study of coronary heart disease in a male population over a 5-year period. Their study showed an association of coronary heart disease with early age of death of father, history of non-cardiac chest discomfort, history of chronic cough, history of shortness of breath, history of peptic ulcer, presence of increased skin fold thickness, elevated blood pressure, AV nicking in the fundi, elevated blood cholesterol, ST & T abnormalities in electrocardiogram and use of cigarettes and coffee.

No correlation was encountered between coronary heart disease and body weight, mean blood pressure, mean blood sugar levels or diet variations (other than coffee).

This study was subsequently reviewed by Paul et al (1335) with respect to the relationship of sucrose intake and coronary heart disease and it was concluded that although individuals having coronary disease did consume slightly more sucrose, the difference was insignificant. They conclude that the etiology of coronary heart disease is complex and there is no simple link with sucrose consumption.

Finegan et al (40A) in clinical retrospective study failed to correlate coronary heart disease with a high intake of sucrose and his work showed a negative correlation between carbohydrate intake and serum cholesterol. Although he recognizes the epidemiological evidence that correlates diet and coronary heart disease, he feels diet is probably a low grade risk factor and emphasizes high-risk factors such as hypertension, cigarette smoking, diabetes mellitus or idiopathic hypercholesterolemia.

Conflicting reports of presumptive correlation between

sugar intake and arteriosclerotic heart disease led Burns-Cox et al (232) in 1969 to repeat earlier studies by Yudkin and others in comparing dietary histories of hospital patients with myocardial infarction with those of other patients or healthy subjects. Medical histories and diagnosis of myocardial infarction, dietary histories and the use of a standard questionary were employed in a study of 80 infarct and 160 control patients. Age distribution, social class, marital status and sugar consumption were noted (the latter data were derived by tabular conversion factors). The relationship between smoking habits and sugar consumption was also noted.

The object of this study was to reproduce the positive findings of Yudkin correlating sugar consumption and myocardial infarction; the object was not attained. Burns-Cox et al. found a stronger association between infarction and smoking than between infarction and sugar consumption, and concluded that data from this and other studies suggested that consumption of refined sugar was not likely to be a major and specific factor in the production of myocardial infarction.

Howell and Wilson (767) compared 1,158 men considered free of ischaemic heart disease with 170 men with confirmed or possible ischaemic heart disease. No correlation in either groups was noted between sucrose consumption and serum cholesterol, white blood cell count, haemoglobin, E.S.R., beta-lipoprotein, or uric acid. Sugar intake and weight gain after 25 years of age also did not correlate.

Soukupova (102A) examined dietary intakes and mortality rates for ischemic heart disease in 33 countries. There was a positive correlation between ischemic heart disease and the separate intake data on calories, fat, protein and sugar for both men and women. She also states that the results only prove correlations and do not prove causal relations.

Bennett et al (13A) reported in 1970 on a study of male hospital patients which showed a correlation between cigarette smoking and sugar consumption. This was related to a correlation of cigarette smoking and consumption of hot drinks. This was further evidence that epidemiologic studies which indicate a causal relation between sucrose intake and coronary heart disease may, in fact, be showing a correlation between cigarette smoking and heart disease and emphasizes the fact that epidemiologic correlations do not necessarily prove a causal relation.

Platt and co-workers (93A) reported on the relationship between dietary sugar intake and arterial disease. Although the 150 patients with myocardial infarction had a slightly higher consumption of sugar than the 275 control patients, the differences were not statistically significant and there was some evidence in one group that increased sugar was due to an association between sugar consumption and the smoking of cigarettes. They conclude that the evidence is "extremely

slender" which would support the hypothesis that high sugar intake is a major factor in the development of myocardial infarction. Yudkin (1938) criticizes several aspects of this study.

Elwood et al (37A) studied large populations of males and females and compared cigarette smoking and sucrose intake with evidence of angenial chest pains (females) and electrocardiographic abnormalities (males) as indications of ischemic heart disease. There was no correlation between evidence of ischemic heart disease and sucrose intake in males and though some increase in sucrose intake was shown for women with evidence of ischemic heart disease, the difference was not significant (p 0.05). There was a positive association between sucrose intake and cigarette smoking for both sexes, but it was statistically significant only in the female sample.

Fidanza (39A) reported in 1973 on an extensive international prospective study on coronary heart disease (CHD). "Chunk" samples of men, aged 40 to 59, from sixteen areas, were studied for years. CHD, serum cholesterol and diet variables were examined for passable interrelationships. Serum cholesterol levels correlated closely with the incidence rate of CHD. There was no correlation between average calorie intake and CHD or serum cholesterol levels. Total fat had a low correlation to CHD and cholesterol levels, but percent of calories provided by saturated fatty acids was highly correlated to both. Total carbohydrate did not correlate with incidence of CHD. There was a high correlation between sucrose intake and CHD cases and serum cholesterol level, but since there was a very high correlation between sucrose and saturated fatty acid consumption is a common nutritional phenomenon, and there is evidence in many areas of a negative correlation between sucrose and CHD and/or a serum cholesterol levels. Fidanza supports the "conclusion that sucrose consumption, per se, has little influence on serum cholesterol levels or CHD incidence rates."

Many researchers have utilized animal models to study the relation of sucrose to heart disease and atherosclerosis, but the lack of suitable models for these conditions has required that animal research direct its attention at the affects of diet on other physiological criteria such as serum cholesterol levels, blood lipid levels, etc. which, in turn, have been implicated in or related to the development of heart disease. Keys (891) questions the "relevance of these short-term experiments to long-term national diets" because "stabilization of serum triglycerides in man, after marked change in the diet, requires many months. He also notes the use of high levels of sucrose in experimental diets equivalent to three or more times that in natural diets.

Alfin-Slater (1A) reports results that do not entirely agree with those reporting generally higher blood lipid values in sucrose fed animals as compared to starch-fed animals. Serum and tissue cholesterol and cholesterol biosynthesis are more affected by fats than by carbohydrates.

"One of the conclusions to result from our study is that it is impossible to define the effects of a particular nutrient from one set of experimental conditions and without due consideration of the other constituents of the diet."

In 1969 Anderson (6A) reported data on animal studies in which sucrose and several starch diets were fed to groups of rats. Sucrose, corn starch, modified maize starch, modified corn starch, modified tapioca starch and modified white milo starch were compared by feeding male weanling rats for 28 days. Sucrose fed animals had significantly lower serum and hepatic cholesterol than animals fed modified starch (cooked or uncooked). These differences also held for sucrose when compared to corn starch although the differences were not always significant.

Brooks et al (18A) presented experimental data on swine fed varying diets to demonstrate the effect of sucrose, fat, mithionine, thiamine, cholesterol and fish meal. There was a high incidence of granulomatous endocarditis in the left atrium in all swine receiving sucrose (approximately 64% of diet) that were held until weighing over 50 pounds. None of the pigs on non-sucrose diets exhibited the heart lesions. Although the lesions were suggestive of infection, allergy or parasites, no causative agent could be found and they were presumed to be due to the high level sucrose intake.

Naismith et al (84A) have studied the hypertriglyceridaemia resulting from high sucrose intake in rats and conclude that hypertriglyceridaemia is caused by sucrose and is not the result of inability to clear this lipid fraction from the blood.

Bruckdorfer et al (20A) reported significant increases in the concentration of total cholesterol and triglycerides in the aortas of rats fed sucrose (68% or 50%) for 160 days, when compared to rats receiving starch in place of the sucrose. Phospholipid content was not affected. He further reported that lactose did not produce a hyperlipaemic effect when fed in a diet where sucrose produced a positive response.

Land and Barthel (67A) reported a study in which high levels (60% of diet, dry weight) of carbohydrate were fed to monkeys for 16 months. Sucrose and dextrin diets were compared in equal groups of monkeys which included Cebus albifrons, Macaca arctordes and Macaca mulatta. Serum cholesterol

and triglycerides were markedly increased in both diet groups, apparently from the sudden change to high carbohydrate diet. Several species differences were noted, indicating possible genetic differences.

St. Clair et al (1495) studied the long-term effect of sucrose and corn starch diets fed to swine for 2 years. The carbohydrates formed 60% of their respective diets and serum lipids, glucose, and insulin were determined and compared to the development of atherosclerosis. No significant differences in serum constituents were noted during the 2 year feeding period. The extent of aortic atherosclerosis was not significantly different after 1 and 2 years on experiment. An increase in coronary artery pathology was noted at 1 year, but not at 2 years. There appeared to be a definite direct relation between atherosclerotic changes and the swine cholesterol level, but these did not correlate with the feeding of sucrose in place of starch.

Grande and Prigge (52A) studied the effect in dogs of 10, 20 and 40% coconut oil in two diet substitutions. In one the oil replaced part of the sucrose and in the other substitution, it replaced part of the protein. Increased oil resulted in elevated serum cholesterol and phospholipids, regardless of the diet substitution. No differences were noted between sucrose and protein diets with equal levels of coconut oil. The authors state that isocaloric exchange of protein for sucrose, whether in the absence or in the presence of CNO, causes no significant change in the serum levels of cholestrol and phospholipids. They also note that the increase in serum triglyceride cannot be attributed to a specific effect of sucrose because previous work has shown that substitution of sucrose for starch at 48% of the diet had no effect on the serum triglycerides level in dogs.

Because of the nature of the material in question, sucrose, and its acceptance as a common food ingredient, there has been extensive experimentation using human subjects. Many articles relating to this section are covered in the review of metabolism.

Little et al (69A) correlated diets of healthy Canadian men and men with coronary heart disease. Initially it was shown that serum lipids and lipoproteins were higher in the coronary group although the diets were essentially the same. When diets were varied within the groups, there was a positive correlation with serum cholesterol, phospholipid and Std S_f 0-20 lipoproteins. Carbohydrate and sucrose had no important correlation with these factors. The control or healthy group tended to have a negative correlation between the same dietary factors and serum lipids and lipoproteins. It was concluded that the coronary-prone man appears to be metabolically different.

Grande et al (641) compared serum cholesterol in man receiving various single carbohydrates substituted isocalorically for carbohydrate and protein of bread and potatoes in their diet. Their results indicated that sucrose and the bread and potato diet produced identical serum cholesterol levels, while the diet containing leguminous seeds (beans, lima beans and split peas) resulted in lowering of serum cholesterol. It was stated that the hypocholesteremic effect of the legumes may be due to other factors than the type of carbohydrate.

McGandy et al (79A) examined the comparative impact of fats and carbohydrates on serum cholesterol in man and concluded that the carbohydrate effects are of a much lower magnitude than the fat effects. Stare (103A) reviewed this data and agreed that the magnitude of effect of carbohydrate source on the regulation of serum cholesterol is too small to utilize dietary carbohydrate alteration in the regulation of blood cholesterol.

Antar (48) in 1968 reported that the isocaloric substitution of sucrose for starches in specific conditions resulted in acceleration of blood coaguability, an increase in serum saturated fatty acid and a decrease in polyunsaturated fatty acids in lecithin. Szanto and Yudkin (1688) reported on the abnormality of platelets in individuals receiving " high-sucrose" diets. Platelets of three individuals which exhibited "sucrose-induced hyperinsulinism" exhibited electrophoretic behavior in the presence of ADP that is characteristic of individuals with atheroschlerosis, while the pattern of platelets was normal for three subjects which did not exhibit hyperinsulinism. Similar results were reported by Yudkin and Szanto (1686) regarding correlation of sugar intake "with platelet adhesiveness and with insulin levels (measured before and after oral glucose)." The correlations of sucrose intake, coronary heart disease, serum insulin levels, obesity and diabetes are further discussed by Yudkin (1937) in support of his hypothesis regarding sucrose as one cause of coronary heart disease.

Little et al (69A) examined nine hyperlipoproteinemic individuals but found sucrose was not definitely hyperlipidemic under the diet and conditions of the first studies, but was more hyperlipidemic than starch when fed in diets high in saturated fats and cholesterol utilized in subsequent studies. In subsequent studies (7A) direct relationship was noted between hyperlipidemic effect and sucrose intake when a diet high in saturated fats and cholesterol was fed.

Yudkin and Szanto (120A) present data relating increased sucrose intake by male individuals shown to be subject to sucrose induced hyperinsulinemia to increases in plasma insulin and fluorogenic corticosteroids.

Nikkila and Kekki (85A) reported the effects of fructose and sucrose on triglyceride metabolism in patients with endogenous hypertriglyceridemia. Sucrose diets produced the most marked rise in serum triglyceride when compared to fructose and starch diets but the limited number of subjects studied do not justify a definite conclusion.

Dunnigan et al (446) studied the effects of sucrose substitution for starch in the diet of middleaged men. They concluded that glucose tolerance, plasma insulin and serum lipids are not significantly altered by the substitution at a level of carbohydrate intake comparable to that found in the Western diet.

MacDonald and co-workers (72A, 73A, 74A, 1054 and 1063) have extensively studied the effect of sugars on hyperlipidemia. Fructose is implicated as the most active as a hyperlipodemia agent and the relationship of sucrose intake and serum fructose levels have been shown positive correlation.

Grande et al (51A) reported the effects of several high carbohydrate foods on fasting serum cholesterol, phospholipid and triglyceride levels. Four groups of young men were given diets containing four different high carbohydrate supplements, namely sucrose, wheat flour, mixed fruits and mixed vegetable, in equi-caloric amounts (500 kcal). Protein was maintained constant. Diets were rotated on a 2 week period basis so each group finally was exposed to each diet. The vegetable diet resulted in much lower serum cholesterol levels than for the other diets which were essentially the same. A similar relationship existed for phospholipids. No significant difference was noted between triglyceride levels of the four groups. In a second similar experiment, comparing sucrose, wheat flour, chick peas and a mixture of dry peas and beans, no significance between diet differences were found.

In an attempt to pull together the various aspects of the attempted correlation of sucrose and heart disease, a number of authors have reviewed the often conflicting studies and evaluated the data.

In 1967 Grande (50A) reviewed the information available on the effect of dietary carbohydrate on serum cholesterol. Although he recognized the concept that replacement of sucrose by starch in the diet resulted in a decrease in serum cholesterol, he stated, "Critical examination of the data at hand indicates, however, the changes of serum cholesterol concentration caused by such dietary exchanges in normal men are usually small and do not always reach statistical significance." This statement on normal individuals is in contrast to information presented on patients with primary hyperlipemia which shows marked changes in serum cholesterol and particularly great changes in serum

triglycerides when starch is exchanged for sucrose in their diet. With regard to animal studies on dietary carbohydrates and serum cholesterol, he concludes that "the facts illustrate the complexity of the problem of the effects of dietary carbohydrates on the concentration of serum cholesterol in animals." He further cautions with reference to epidemiological studies that the conflicting information on carbohydrate-serum cholesterol interrelations "must serve as a reminder of the principle that statistical correlation does not necessarily mean a cause and effect relationship."

Walker (1839) in a 1971 review on sugar intake and coronary heart disease (CHD) (bibliography includes 104 references) presents a very thorough evaluation of the information to date. He lists the following criteria needed to be used in order to incriminate sugar: "(1) Accurate data on sugar intake in total populations and in sub groups. (2) Corresponding data on CHD prevalence, incidence or mortality rate. (3) Unequivical demonstration that in propitious circumstances the lowering of sugar, involuntarily or voluntarily, is specifically associated with a fall in the frequency of CHD or its associated risk factors. (4) Information on the response of experimental animals to sugar in a variety of contexts. (5) Knowledge of the metabolic mechanisms which deals with sugar and their physiological and pathological sequelae."

Applying this criteria of evaluation to each aspect of the question such as CHD and population groups, random samples of population, special populations, voluntary and involuntary changes, animal studies and mechanisms of metabolic response, the following conclusion is drawn. "Firstly, although evidence is incomplete, such evidence as is available does not significantly incriminate sugar. Secondly, bearing in mind the multifactorial etiology of CHD, it is questionable whether, within a given context, major incrimination of sugar is possible. Thirdly, more intensive research on particular minority groups in Western populations might provide more trustworthy inferences."

Walker (111A) commenting on the use of international comparison of data on diet and coronary heart disease cautioned that researchers will find particular situations which do not fit a hypothesis and must be taken into account.

DeSilva Abiaka (36A) presents a limited review of the relationship of sucrose consumption and the incidence of cardiovascular disease in which sucrose is incriminated to some degree, but a number of statements are presented that would appear to conflict with information as presented by other authors.

In 1971 Keys (63A) reviewed the available studies theorizing that sucrose in the diet is a major factor in the

development of coronary heart disease. It is his conclusion that the theory is not supported by acceptable clinical, epidemiological, theoretical, or experimental evidence. He presents counter arguments to the epidemiological studies on which Yudkin has based his hypothesis, questions the significance of the sucrose effects on fat metabolism in short-term experiments and emphasized the mass of data indicating high levels of sucrose intake do not increase serum cholesterol.

Ahrens (1aA) in his review reached quite the opposite conclusion as that drawn by Keys (63A) and seriously concludes that sucrose consumption is related to heart disease.

Hegsted and Stare (56A) review the information on sucrose intake and its relationship to cardiovascular disease and conclude that present experimental information on the effect of high sucrose diets must be tempered by the fact that some populations consuming high levels of sucrose do not support the experimental findings. They do not feel the epidemiologic data is conclusive as to a relation between the intake of sucrose and cardiovascular disease. They concede that the synergism between sugar and saturated fats in raising serum triglycerides deserves very careful study, preferable long-term studies which simulate natural conditions and practical diets.

In 1972 Yudkin (117A) presented a general discussion of his hypothesis that sucrose is one of the causative agents of ischemic heart disease and suggests that combined evidence of several types is important in proving his hypothesis. He presents positive information relating ischemic heart disease and sucrose intake from epidemiologic experimental data and association with related diseases. In another article in 1972 Yudkin (118A) reviews correlations and data relating sucrose intake to obesity, caries, seborrheic dermatitis, myopia, accentuation of protein deficiency, diabetes, ischemic heart disease, and gout. The ability of sucrose to affect this wide varience of diseases or conditions is explained by its affects on hormone secretion (insulin and corticosteroids) and changes in tissue enzymes.

In 1970, because of the acute interest in nutrition and disease, the British Department of Health and Social Security set up a panel to advise on the significance of any relation between nutrition and cardiovascular and cerebronascular disease. The panel spent three years evaluating the data and preparing a report. In the section on dietary carbohydrate and risk of ischemic heart disease, it is concluded that the evidence against sucrose is inadequate and confused by the complexity of alterations encountered in the epidemiologic studies.

IX. Sugar Intolerance and Allergenicity

The inherited absence of intestinal sucrose was reported by Burgess et al (231) in 7 cases in which jejunal mucosa biopsies showed an enzymatic deficiency in sucrose which was distinguishable from an acquired carbohydrate intolerance resulting from disease involving the small intestine. The absence of intestinal sucrose results in severe diarrhea following ingestion of sucrose and an inability to metabolize sugar as shown by the presence of the carbohydrate in the urine and feces after oral ingestion of sucrose. The authors suggest that cases of hereditary sucrose intolerance are not uncommon. Seven case histories are described in detail and the authors present a discussion of the basis for suspecting the hereditary nature of the condition.

An anomaly consisting of a congenital incapacity to eat any kind of sweet food was reported in a paper by Davidenkov (382) in the Journal of Heredity, 1940. Two series of brothers and sisters contained members unable to eat sugar in any form: one series of 7 children had 2 cases of aglycophagia; a second series of 5 children had 4 affected with the anomaly, which in all cases appeared in early childhood and persisted throughout the lifetime of the affected individuals. Efforts of the aglycophagic individuals to swallow sweet foods resulted in nausea and unpleasant physical weakness. The degree of aglycophagia was not total in all cases but appeared somewhat milder in several instances. Non-sweet polysaccharides were not rejected, suggesting that the abnormality was not due to disturbed carbohydrate metabolism.

Four cases of allergic symptoms attributable to sucrose were described by Randolph and Rollins (1409). A variety of clinical allergic responses were observed which are referred to as the fatigue syndrome of allergic origin, or allergic toxemia: myalgia, mental confusion, depression, extreme fatigue, nervousness, tenseness, and so-called "jitteriness". In each of the cases described, the patient was unaware of the role of dietary sucrose in the allergic symptoms due to typical masked type of food allergy. With the avoidance of sucrose, allergic symptoms were either absent or greatly relieved. The presence of dextran as a contaminant of sucrose has been suggested as responsible for sugar allergy, but this has not been clearly demonstrated. Immunological studies were suggested by the authors for clarification of the nature of sugar allergy: sucrose has been shown to be immunologically active and shows a positive precipitin reaction when tested against Type 2 pneumococcus antiserum. Invert sugar of cane origin when injected intravenously causes allergic responses in many cane-sensitive patients.

A report by the same authors (1410) describes cases of beet sugar sensitivity and a sensitivity to monosodium glutamate derived from beets. A point is made by Randolph and Rollins regarding the failure of federal labeling regulations to differentiate the types of sugar used in processed

foods, which may be of some consequence to individuals sensitive to one or more of the different sugars employed (this was written in 1950). The allergic manifestations of beet sensitivity are similar to those noted in the preceding report: Myalgia; fatique; various mental symptoms; and asthma, rhinitis, urticaria, dermatitis, headache and gastrointestinal symptoms.

An apparent tolerance to high levels of sugar intake is reported by Campbell and Goldberg (24A) who examined sugar cane workers that can consume up to 3 lb. of sugar without apparent ill effects. After ingestion of an experimental dose of 1 to 2 pounds, workers examined did not demonstrate glycosuria or other ill effects.

X. Skin and Skin Lesions

Yudkin (118A) reported that patients with seborrheic dermatitis consumed significantly more sucrose than other individuals their same age. He also reports a swine feeding study where swine on high sucrose diets developed dermatitis. Bender (11A) refers to reports that lipid content of skin sebum was different when individuals were on high sucrose diets in comparison to high starch diets. MacDonald (1054) also suggests that that effect of carbohydrate on fatty acid proportions may be justification for the association of acne and high carbohydrate consumption.

XI. Obesity

Excess weight gain and high consumption of sucrose have been associated in the scientific literature, lay press and peoples mind for many years. In recent years, the emphasis on weight control and the advent of artificial non-caloric sweeteners have greatly emphasized the importance of sugar as it relates to obesity.

Visser (110A) reports that high levels of sucrose in the diet of rats caused no increased weight, no increased soft tissue, (fat and muscle), no glucosuria, no effect or calcium content of bone, no vitamin deficiencies, no increase in body fat. It is suggested that sugar is shown to be not fattening.

Bray (17A) reports on the comparative effectiveness of diet practices used for weight reduction. He emphasizes that decreased food consumption alone was generally successful in treating obesity.

Friedhoff et al (569) studied the comparative effect of water, sucrose solution and no caloric sweeteners on weight gain in mice. No difference between any pair of diets was noted and the effectiveness of non-caloric beverages in weight reduction is questioned.

It is questionable that data on animals on free-choice food consumption can be compared to anticipated results in a human population. Animals generally are expected to adjust to free-choice feeding and not overeat while humans have, apparently, other psychological aspects to appetite and eating that allow them to eat more than required with a resultant prevalence of obesity. However, it has been reported by Richardson (96A) that studies on a population of businessmen showed a definite inverse relationship between sugar intake and body weight. A positive association between sucrose intake and cigarette smoking was related to an extremely low sugar intake by ex-smokers.

XII. Diabetes

Diabetes is functionally directly related to carbohydrate intake. Etiologically the relation is vague. The correlation of diabetes to other physiologic factors has been examined by Erlander (38A) and diet deficiencies related to the development of diabetes.

Patel et al (91A) described the problem of attempting to curtail carbohydrate intake in diabetics of India where they have a primarily vegetarian (high carbohydrate diet). It was shown that high carbohydrate intake allowed good regulation of diabetes with moderate limitation of caloric intake.

Brunzell et al (22A) supports the concept of carbohydrate diets for diabetics showing that higher carbohydrate intake improved glucose tolerance and lowered fasting plasma glucose levels.

Bierman et al (15A) also describes a dietary schedule for diabetics which includes high carbohydrate and low fat and cholesterol and proposes that the average percent of carbohydrate in the diet of the U.S. population (45%) is probably acceptable for the diabetic.

Finally Keen (60A) reports on sucrose as the carbohydrate consumed and reaches similar conclusions that increased sucrose intake is not detrimental with respect to glucose tolerance and with clinical studies and epidemiologic surveys presents evidence that increased sucrose intake is not etiologically related to the development of diabetes.

XIII. Sucrose and Nutrition

It seems only logical to terminate the review of the biological aspects of sucrose that some reference be made to the physiological functions of sucrose which is nutritional as a source of energy and the glucose molecule.

Fewkes et al (514) reviews the character, function and importance of sucrose in biological systems as a major product

of photosynthesis and the mobile source of energy in plants and/or one of the world's leading commodities. He reviews sucrose from the viewpoint of the chemist, the plant physiologist and the food technologist.

Refering to sucrose as food stuff, Fewkes (514) states that it is a source of energy and carbon for cell tissue building, but is not an essential nutrient. Apart from the nutritional value, sucrose is also important as flavoring in a wide variety of foods such as fruits and juices, beverages, vegetables, pickles, etc. which make it of further importance nutritionally. It is also important as a preservative for jellies, jams, preserved fruits, and condensed milk for its physical properties to provide texture, body, viscosity and moisture retention. Although these last items are not related to biological properties, the improved palatability of the foods affected is important to the nutritional well being of the human population and while functioning as a flavor, preservative or physical agent, it is also acting as an excellent source of energy.

Naismith and Cursiter (84A) show the essential nature of carbohydrate in the diet as an energy source for protein sparing effect. Consolazio et al (30A) and Gollnick (48A) report on the importance of carbohydrates to the body under stress conditions. Benade (122) presents data on the physiologic response and improved condition in mine workers which were given a mid-shift feed of sucrose.

Biochemical Aspects

1. Breakdown

Sucrose in solution undergoes hydrolytic decomposition in the presence of hydrogen ions. The transformation of dextrorotary sucrose to a levorotary mixture of monosaccharides, D-glucose and D-fructose, is called inversion, and the equivalent mixture of monosaccarides is known as invert sugar. In living organisms the hydrolysis of sucrose is catalyzed by glycosidases, and the invert sugar may be fermented to alcohol, lactic, butyric and acetic acids, etc. In addition to hydrolysis, other biochemical reactions are known: alcoholytic, glycerolytic, phosphorylytic and arsenolytic decomposition of sucrose. Certain bacteria, such as species of Leuconostoc, may form polysaccharides from sucrose, of which dextran is important; dextran is composed of D-glucose units and forms jelly-like masses during beet sugar production, clogging filters and retarding crystallization. The final result or breakdown of sucrose in the digestive process is the total oxidation into carbon dioxide and water, liberating the energy utilized in the plant photosynthesis of sucrose; nutritively, this energy is expressed as 3.95 k cal/g.

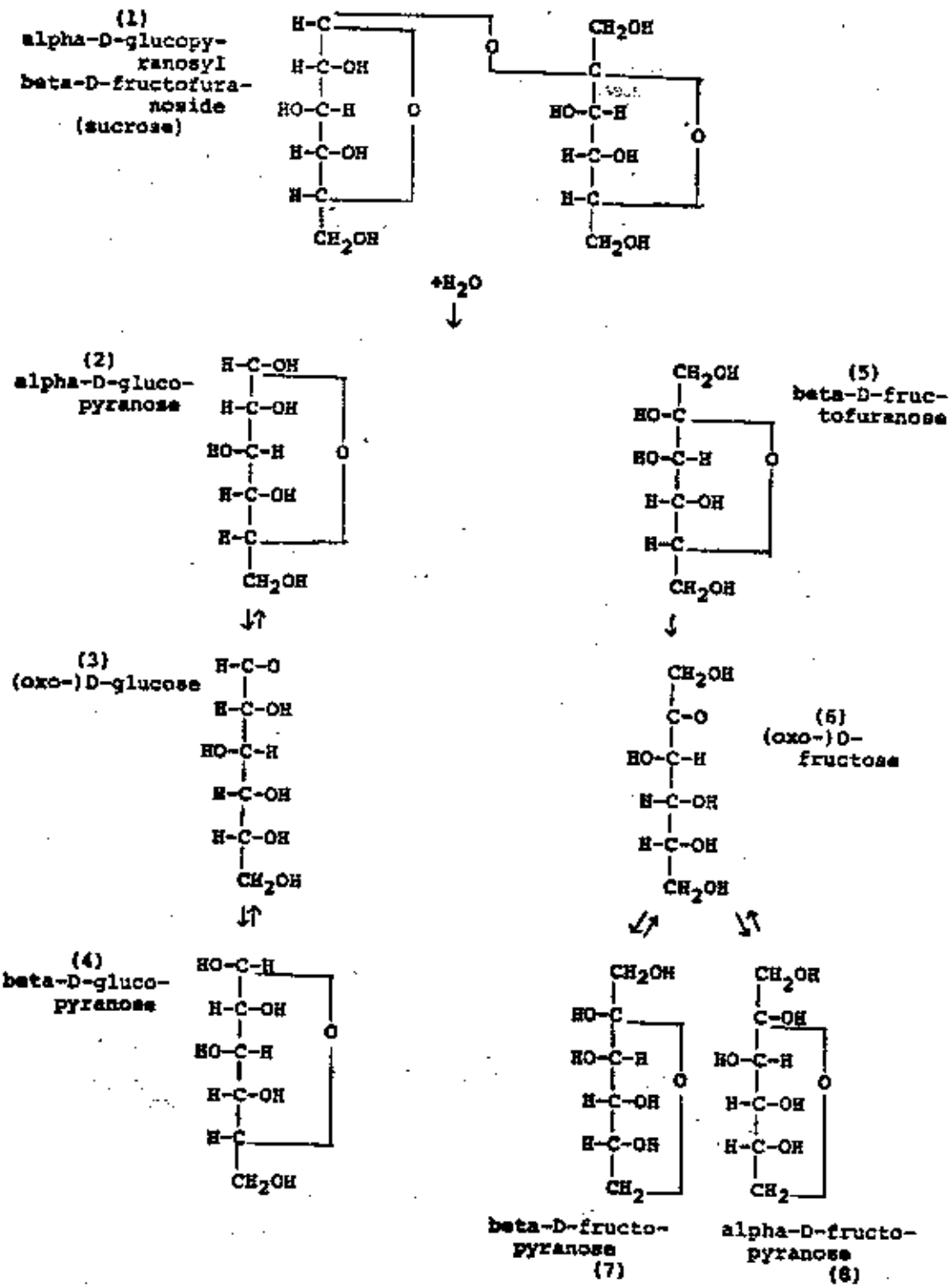
The inversion of sucrose is shown by the diagram on the following page:

II. Absorption - Distribution

A report by Akinyanju et al (18) of a comparative study of starch and sucrose diets in young male volunteers noted sucrose in the urine during intakes of 500 mg/day sucrose but not when starch was ingested. There is no significant absorption of unhydrolyzed sucrose and if injected intravenously, it is excreted quantitatively in the urine. Sucrose is therefore, hydrolyzed prior to or at the site of absorption. Acid hydrolysis in the stomach does not occur. Invertase (alpha-glucosidase), present in the intestine very early in fetal life, is not markedly affected as to level of sucrose consumption; being present at about the same level in populations having low or high carbohydrate consumption. Dahlqvist (33A).

The textbook version of the metabolism of disaccharides which portrays the disaccharidases as being secreted with the intestinal juice into the lumen of the small intestine is not true, according to Dahlqvist (364) in a review paper. The digestion of disaccharides occurs intracellularly in the wall of the small intestine. Dahlqvist describes a number of studies which have led to the intracellular concept of disaccharide digestion. Three principal methods have been employed: tissue fractionation methods; in vitro incubation with intestine; and histochemical staining of enzyme activity.

(Inversion of sucrose)



Dahlqvist (33A) summarizes this enzyme theory with the following table:

Table I. Disaccharidases and glycosidases in the small intestine. The brush border enzymes account for the digestion of dietary disaccharides, while the soluble and lysosomal enzymes probably have other functions.

A) Brush border enzymes
   1) Isomaltase: This enzyme also hydrolyzes maltose, and accounts for about 50% of the total maltase activity.
   2) Invertase (=sucrase): Also this enzyme hydrolyzes maltose, and accounts for about 25% of the total maltase activity.
   3) Heat-stable maltases.
   4) Lactase.
   5) Trehalase.

B) Soluble or lysosomal enzymes
   1) Acid beta-galactosidase.
   2) Hetero-beta-galactosidase.
   3) Acid alpha-glucosidase.

He also points out that there is an active transport mechanism for glucose, and probably for fructose, too, involving a relation between sucrose and a specific membrane caries for glucose released from sucrose during hydrolysis.

MacDonald and Turner (1063) have presented data comparing serum fructose and glucose levels after a meal of sucrose and after a similar meal composed of a mixture of glucose and fructose equivalent to the sucrose meal. Serum glucose levels were not different but fructose levels were higher when the disaccharide was fed than when the monosaccharide mixture was ingested. Crossley and MacDonald have shown that serum glucose levels after a sucrose meal are affected by chronic feeding of high level sucrose diets while fructose levels in portal plasma were significantly increased. These facts indicate a difference in fructose and glucose absorption and also differences related to whether they come from sucrose digestion or are fed as monosaccharides. Dahlqvist (33A) refers to "transport mechanisms" as a factor. The different molecule configuration of fructose immediately after sucrose hydrolysis and fructose that has been in solution as the monosaccharide.

III. Metabolism and Excretion

As noted in the preceding section (Absorption-Distribution), sucrose is split into glucose and fructose at the surface of the intestinal mucosa and does not normally appear

in the tissue as sucrose. The metabolism of sucrose, is - then, that of glucose and fructose. Glucose is absorbed and largely metabolized in the extra-hepatic tissues for energy, tissues or cell component synthesis or stored as glycogen or fat. Fructose is predominently metabolized by the liver where it is converted to glucose, glycogen and triglycerides.

IV. Effects on Enzymes and Other Biochemical Parameters

Anderson (44) reported on a specific nephopathy which developes after injection of sucrose systemically. This is of significance only where sucrose is injected as in therapeutic procedures. Rosenmann et al (1464) fed high levels of sucrose and starch diets for nine to eighteen months to rats. Comparing sucrose to starch fed animals, sucrose fed animals showed decreased body weight gain, impaired glucose tolerance and increased incidence and severity of nephropathy.

In an extensive experiment, Bender and Thadani (124) investigated the metabolic differences between sucrose and starch in the rat and found that dietary sucrose depresses the rate of oxidation of glucose and of lipogenesis from glucose in both liver and adipose tissues. It was suggested that the effects observed may have been due to increased levels of various enzymes and consequent changes in the metabolic pathways. The experiments were conducted on diets containing 60% carbohydrate (glucose or corn starch). Numerous researchers have studied the effect of sucrose consumption on glucose tolerance. Anderson et al (5A) reports that there is direct evidence in the literature to show that glucose tolerance deteriorates in rats and men fed high levels of sucrose. Their own experiment on 11 normal men indicated a diet fed containing 80% sucrose resulted in an improved glucose tolerance test (GTT) when compared to GTT on subjects being fed 80% glucose in their diet. This agrees with reports that indicate improved GTT with high carbohydrate diets. The improved GTT in the face of lowered plasma insulin values reported suggests that high carbohydrate diets may increase insulin-sensitivity of the individuals (22A).

The relationship of sucrose intake and serum triglyceride levels has been reported extensively. The reader is referred to the previous section, Biological Effects - Heart Disease, for reference to some of these articles.

A high sucrose diet given to nineteen healthy men during a study by Szanto and Yudkin (1686) produced no change in levels of blood cholesterol or phospholipids, but did increase significantly the triglycerides.

In a study by Mann et al (77A) no differences were noted in triglyceride levels when normal diets containing sucrose

(23% of total calories) was replaced isocalorically by starch. There were also no differences in fatty acid patterns when diets were changed. A low carbohydrate diet did result in decreased triglyceride concentrations and increased cholesterol levels.

In a report by Cahlin et al (23A) high sucrose intake (800 Kcal per day) resulted in elevated plasma triglyceride when fed to normolipoproteinemic patients while less significant triglyceride increase was noted in prebeta hyperproteinemia. The change in the normal individuals are explained by the assumption of an initial influx of triglycerides exceeding clearing capacity and followed by a period when clearing capacity is enhanced and triglyceride levels drop toward the initial level. A steady state with a higher turnover may presumably be the normal result. These results are supported by the data in the abstract by Muller (82A).

Bruckdorfer et al (21A) could not support the suggestion that effects of dietary sucrose with respect to lipid changes were due to chromium deficiency.

MacDonald (72A) (73A), Mann (77A) (78A) and Roberts (97A) are additional references on the relation of sucrose and serum lipids.

The interrelation of sucrose feeding and insulin has been referred to in a previous section, Biological Effects-Diabetes.

Barter et al (9A) reported plasma triglyceride, free fatty acid and insulin diurnal fluctuations in subjects receiving their total calories from sucrose for 2 or 3 day periods. Plasma free fatty acids and triglycerides rose during the night and fell during the day while insulin rose during the day and fell overnight: It is suggested that the inverse relation between triglyceride and insulin may not be inconsistant with the many reports of positive correlation between triglyceride and insulin levels. Several proposals are presented to explain the apparently conflicting results.

Taube et al (68A) reported on the effect of isocaloric starch and sucrose-rich diets fed to rats on glucose tolerance and insulin response. Compared to starch feeding, feeding sucrose-rich diets (70% sucrose) resulted in marked hyperinsulinemia following oral or intravenous tolerance tests. The glucose disappearance rate is only increased following intravenous glucose tolerance tests. In this study, prolonged high level feeding of sucrose appeared to have a direct insulinotropic effect. Mann and Truswell (77A) in a human study did not find any significant differences between fasting serum levels of immunoreactive insulin or in insulin response when subjects received sucrose supplements compared to subjects on starch supplements which were fed at levels normally consumed and in mixed diets.

Moser and Berdanier (81A) recently reported experiments in which rats were fed 65% sucrose or 65% starch in their diet until 50 days of age at which time half the sucrose fed animals were switched to starch and half the starch fed animals were switched to sucrose. Sacrifices were scheduled and animals examined at 50, 100, and 142 days of age. Their results indicate that the type of carbohydrate fed in early life may have long lasting effects on the metabolic patterns of rats even though the carbohydrate source is changed.

V. Drug Interaction

None observed in literature reviewed.

VI. Consumer Information

The widespread use of sugar as a nutrient, preservative and for flavoring and physical effects on foods was referred to in Biological Effects-Sucrose and Nutrition. The reader is directed to Fewkes (514) and Yudkin (1932) for information on consumption levels. The U.S. consumption is approximately 100 pounds per person per year and has remained essentially constant for 50 years (Stare 104A).

Summary

Sucrose is the most abundant carbohydrate found in the sap of land plants. It is essential to the mobile transport of energy within the plant. It has been produced from sugar cane since 2000 B.C. and from sugar but since early 1800's. It is available in essentially pure crystalline form in large quantities. The 1972 world production of total sucrose was 83 million tons, coming primarily from cane and sugar beets and in very limited extent from sorghum and maple.

Sucrose functions in the human diet as a carbohydrate, and is classed as a simple carbohydrate with other sugars such as glucose and fructose in comparison to the complex carbohydrates such as starches from corn, potato, or wheat. Carbohydrate provides a major percentage of the caloric intake for the populations of the world. Variation of intake depends on availability within specific countries, and ability to purchase on the world market. Although sucrose utilization is frequently said to be related to the affluent societies, the correlation between sugar consumption and degree of affluence does not stand up when all countries are considered.

Sucrose is utilized in the food industry as a basic nutrient (carbohydrate) source, as a sweetner, for imparting particular physical characteristics to foods and in food preservation. Of the eleven million tons consumed in the United States, approximately 24% is sold in consumer-sized packages and the remainder is utilized in the food industry. Non-food use accounts for approximately ninety thousand tons.

The biologic effect of the consumption of the disaccharide, sucrose, is basically the effects of glucose and fructose, the monosaccharides into which it is split by enzymatic action in the digestive tract. Glucose provides energy and structural components for the animal body. Fructose is converted to glucose in the liver and then essentially functions as a glucose molecule. There have been subtle differences noted between the effects of consuming the disaccharide, sucrose, and the effects of consuming an equivalent amount of its monosaccharide components, glucose and fructose as a mixture. These differences are involved in the present attempts to determine if a high level of sucrose in our diet is potentially detrimental to human health.

Although an acute toxicity response can be obtained on administration of very high doses of sucrose, such quantities have little application to anticipated exposure. Subacute and chronic toxicity of sucrose also has not been shown to be a concern, per se, but certain conditions which are generally related to metabolic inadequacies of the individual (diabetes, disaccharide intolerance, etc.) result in an apparent toxicity of

sucrose for specific individuals. In recent years considerable controversy has centered around the relationship of sucrose to 3 major problems of human health, namely, obesity, caries and coronary heart disease.

Although the general concern regarding the relation of sucrose consumption and obesity centers on the hypothesis that sugar is a material that is more apt to be eaten beyond satiety than other calorie sources, there is some evidence that high sugar diets do not generally correlate with obesity. Both experimental and epidemiological evidence exists showing inverse correlation between obesity and sugar consumption.

The occurrence of caries is dependent on the consumption of carbohydrates and sucrose appears to be one of the most cariogenic carbohydrates. The incidence of caries is not dependent on only the presence of carbohydrate or sucrose, but the form in which it is present (sticky mass) and the frequency of administration (between meals and bedtime snacks) are particularly important. Present research on prevention of caries includes extensive effort on the definition of the oral microorganisms and their relation to caries, their dependence on sucrose, antibiotic and immunologic control of the microorganisms, and natural anticaries agents in other food stuffs.

By far the most heated controversies surround the question of sucrose as an etiologic agent in the development of coronary heart disease (CHD). This controversy was initiated by epidemiologic studies showing correlation between increased sucrose intake in populations with an increased incidence of CHD in the same populations. The questions asked related to the frequently weak correlation and the presence of other changes that correlate with sucrose intake, such as cigarette smoking and coffee consumption, which are considered by many to be etiologically related to CHD. It is frequently emphasized, as well, that statistical significant evidence of correlation only proves the correlation and does not prove a causal relationship. The presence of populations in the world that show an inverse correlation between the consumption of sucrose and incidence of CHD further confuse the picture.

Equally diverse are the results and opinions on the experimental and clinical research. Since there is no adequate model for CHD in experimental animals, much of the research on animals is directed at other physiologic parameters that are related to CHD such as serum cholesterol, serum triglycerides, other blood lipids, insulin levels, etc. The results appear to vary widely, frequently due to wide variation in procedures such as test levels, duration of study, species and strain, and other elements in the diet to mention some of the major ones. The use of high levels of test material in comparatively short-term studies to evaluate effects of a nutient material (obviously having

biological activity) which is to be consumed at lower levels for a lifetime is seriously questioned. Also testing nutrients in other than a near normal dietary environment also can produce interesting but inapplicable data for safety evaluation of the nutrient. This applies to protein, fats and starches as well as to sucrose.

The clinical studies have much the same problems of diversity and evaluation as do the animal experiments. They are generally short-term and frequently utilize abnormal levels and diets which do not allow the human subjects to stabilize. In either animal experimentation or clinical research, the results and effort, very briefly summarized, show the consumption of sucrose under specific conditions can effect the blood lipids, insulin response and metabolism, and other lesser studied responses related to CHD. There are studies that show no effects. What appears to be lacking are indepth studies involving long-term feeding of sucrose and starch at reasonable levels in a normal diet combination to normal subjects. The evaluation of the effect of sucrose consumption in metabolically different subjects (diabetics) should be a separate study and information from such studies may be of limited value in evaluating the safety of sucrose in the general population.

What is not lacking is a wealth of literature related to the subject. A number of reviews, (50A)(1839)(11A)(36A)(63A)(56A)(117A) and (1aA), present the pros and cons in some detail. Among the more recent reviews, Keys (63A) presents a more positive evaluation of sucrose while Ahrens (1aA) presents a more negative evaluation.

The evaluation of the place of sucrose in our diet can not omitt its relationship with other nutrients in normal use. There must be a concurrent evaluation of other sugars which might be utilized as substitutes, of the impact of other energy foods (fats and starches) which would be required to replace any decreased availability of sucrose, and of the availability of adequate supplies of these alternate foods. Just as the evaluation of the effect of high level or increasing consumption of a major nutrient (protein, fat, carbohydrate) is not a simple cause and effect problem, the evaluation of a major change in the diet is also very complex.

(Reference numbers not followed by the letter A begin on Page 50.)

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